BACTERIOLOGICAL REVIEWS
Vol. 28, No. 4, p. 490–492 December, 1964

FOOD-BORNE VIRUSES AND MALIGNANT HEMOPOIETIC DISEASES[1]

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As the experimental evidence grows indicating a viral etiology for numerous types of leukemia, lymphoma, carcinoma, and sarcoma in mammals, and birds, it seems less than likely that man will be an exception and not develop neoplasms as a result of antecedent viral infection. Dr. Martin has given a masterful review of the evidence thus far which implicates viral causation of some human neoplasms among which leukemias, especially of the lymphocytic type, and lymphoma are most likely candidates.

However, it is well to emphasize that man is not an inbred species like many of the mouse, rat, hamster, and rabbit strains utilized in viral carcinogenic studies. Homozygous inbred animals appear to be more susceptible to oncogenic viruses than "wild" noninbred heterozygotes. Furthermore, the opportunities for massive inoculation of virus via a nonphysiological route into the newly born occur less frequently in man than under experimental laboratory conditions. However, in the avian leukoses and in bovine and porcine lymphosarcoma, natural epidemiological experiments exist, in which spontaneously transmissible malignant tumors occurring in species living in symbiosis with man are available for study, as Clemmeson has pointed out (2). These disorders may give rise to food-borne viral cross-infection of young children or infants, particularly since the highest incidence of bovine lymphosarcoma occurs in the older dairy cattle (9, 15). Milk has been incriminated as a possible vector, in addition to diseased tissue and intra-herd contact (18). Rosenberger in Germany obtained suggestive evidence of the infectivity of milk from cows with lymphosarcoma for calves born of lymphosarcoma-free cows (18). Papparella in Italy (12, 13) and Dutcher in New Jersey (4) both obtained evidence for a replicating interferon-producing filterable agent in tissue cultures inoculated with bovine lymphosarcoma.

The Middle Western states, including the Southern plains area and the states around the Great Lakes, are known to be among the areas reporting the most bovine leukosis to the U.S. Department of Agriculture (15). We have been able to trace diseased beef cattle back to auction areas in western Iowa and eastern Nebraska.

In Nebraska, we have come to recognize that all forms of leukemia and malignant lymphoma are highly prevalent in our human population, increasing in frequency since World War II, along with the rest of the world (11). The majority of our 1.4 million population still lives on farms or in small villages below 2,500 in size. Recently, George Pickett of our State Health Department observed that nearly one-half of death certificates of male leukemia victims aged 40 to 60 collected statewide over a 5-year period specified farming as the principal occupation. This is more than twice the probable incidence of this occupation in males in this age group. In contrast, male lung cancer deaths in the same group specified farming as the primary occupation in only 20% of deaths reported in this age group (14). An intensive study of the incidence of all leukemia and lymphosarcoma in a six-county area in central Nebraska now underway has revealed at least 20 to 30% under-reporting of leukemia-lymphoma deaths to the State Health Department via death certificates, judging from hospital and office records of the practicing physicians in the area.

In the city of Kearney in the center of this six-county area, Robert Rosenlof, Associate of our Department of Internal Medicine, has noted that leukemia and lymphoma admissions to the Good Samaritan Hospital over the same 5-year period outranked, in number of patients admitted, all other individual types of cancer with the exception of carcinoma of the colon and rectum (14). In addition, he has accumulated observations of seven families with two to three multiple cases of these diseases occurring in both geneti-

[1] A contribution to the symposium on "Current Progress in Virus Diseases" presented as part of the program for the Centennial of the Boston City Hospital, 1 June 1964, with Maxwell Finland serving as Consultant Editor, and John H. Dingle and Herbert R. Morgan as moderators.

cally related, as well as genetically nonrelated, relatives. We have also seen examples of serial involvement of siblings with lymphoma at the University of Nebraska Hospital in Omaha. Similar families with multiple cases of leukemia and lymphoma have been reported from Kansas (10), Ohio (3), Indiana (8), and Minnesota (1), and have served as in our cases to stimulate further investigations into the genetics and virology of leukemia and lymphoma in man. Do these cases represent genetic predisposition, or response to a common viral exposure 1 to 4 decades previously? We would like to know.

The prevalence of these disorders in a largely rural population has increased suspicion of possible cross-infection of humans from enzootic malignant lymphoma and leukemia which has been known to be widely disseminated in poultry flocks and pig and dairy cattle herds in the United States and Europe. Some of Dr. Rosenlof's patients have killed and dressed their own leukosis-infected chickens with their bare hands over a period of years. The amount of chicken leukosis virus contaminating fresh eggs in our refrigerators may be an important question, since in many areas up to 30% or more of chickens and turkeys in flocks may be infected, judging from serological surveys. There are numerous examples of oncogenic viruses being capable of infecting multiple alien species, of which polyoma virus is an example.

Under natural epidemiological conditions, only a small percentage of individuals may develop overt neoplasms long after infection has occurred, although the majority of the cattle herd or poultry flock may by that time have hematological or serological manifestations of viral infection. Thus, a low tumor incidence rate characterizes an exposed population, compared with other types of infectious diseases. The leukemia cluster reported from Niles, Ill., in 1957–1960 resembled an infectious entity, since all the involved children either attended or had siblings attending a parochial school. No cases were reported among the remaining population of public school children in the community (6).

It should also be recalled that the temperature of milk pasteurization is of borderline lethal effectiveness for the relatively heat-stable papova virus group of double-stranded deoxyribonucleic acid viruses. These include most of the known oncogenic viruses, such as polyoma virus, S.V. 40 virus, adenovirus types 12 and 18, human and rabbit papilloma virus, etc. (7). The wide use of milk and milk products, and eggs for infant and juvenile feeding, in Australia-New Zealand, North America, and Western Europe is well known. It is in these areas that reported leukemia and lymphoma incidence and mortality rates are among the highest in the world. In the United States, Minnesota and Vermont have the highest reported leukemia mortality rate and are both among the top dairy production states (11).

Other epidemiological data also suggest a dietary or environmental factor in malignant neoplasia of hemopoietic and lymphatic organs. Among the Japanese in Japan, mammary cancer, lymphosarcoma, and leukemia have been reported far less frequently as causes of death than in the United States (2, 16). The Japanese in the past avoided use of dairy products in their diet, and today less than 10% of the Japanese food budget consists of dairy products, in contrast to 25 to 30% for the United States (5). When Japanese emigrated to Hawaii or California, the death rate from mammary cancer remained low among their female descendants, but in both sexes a two to fourfold increase in mortality has been reported for leukemia and lymphosarcoma, attaining rates comparable to those present among the Caucasian population (16, 17).

In summary, therefore, as a working hypothesis for further investigation, we believe that milk-borne and egg-borne viruses may be highly important in the pathogenesis of human leukemia and lymphoma. Unsterilized foodstuffs may reach the infant very readily in the present state of our hygiene, and numerous uncontrolled rural viral sources are identifiable, which might provide for both urban and rural infection of young children.

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